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Satoskar, Kale, Bhandarkar's

PHARMACOLOGY AND PHARMACOTHERAPEUTICS

FOURTEENTH EDITION

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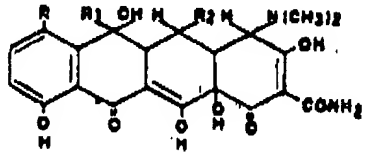
45 Tetracyclines, Chloramphenicol and Antifungal Agents

Tetracycline antibiotics were discovered as a result of a systematic plan by the American Pharmaceutical Industry for screening a multitude of soil micro-organisms for potential antibiotic activity. The first member chlortetracycline, isolated from *Streptomyces aureofaciens*, was introduced in 1948. This was followed by oxytetracycline derived from *Streptomyces rimosus* in 1950 and tetracycline prepared by catalytic hydrogenation of chlortetracycline in 1953. Many other semi-synthetic tetracyclines have since been introduced in the therapy.

Tetracyclines

Chemically, the tetracyclines are naphthacene derivatives. The naphthacene nucleus is made up by fusion of four partially unsaturated cyclohexane radicals and hence the name tetracyclines (Fig. 45.1). The various tetracyclines differ only slightly in structure. The crystalline basis of these compounds are pale yellow, slightly bitter and sparingly soluble in water. However, they form water soluble sodium salts. The acid salts are more stable in the dry powdered state and are usually preferred in therapy. Tetracyclines are more stable at acid pH.



	R	R_1*	R_2*
TETRACYCLINE	H	CH_3	H
CHLORTETRACYCLINE	Cl	CH_3	H
OXYTETRACYCLINE	H	CH_3	OH
DEMETHYLCHLORTETRACYCLINE	Cl	H	H

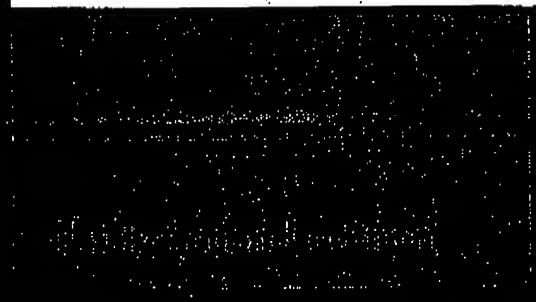
There is no OH attached to the carbon atom to which R is attached.

Fig. 45.1 : Basic structure of tetracyclines

Antibacterial activity: Tetracyclines and their semi-synthetic derivatives have similar antibacterial activity. These drugs are essentially bacteriostatic and along with chloramphenicol are termed 'broad spectrum antibiotics', as, in addition to their antibacterial activity against a number of Gram-positive and Gram-negative organisms, they also inhibit the growth of certain actinomyces (fungi), rickettsiae and chlamydia organisms. Gram-positive organisms in general respond better than Gram-negative organisms.

The Gram-positive and Gram-negative organisms inhibited by tetracyclines include Pneumococci, Gonococci, some strains of *alpha* and *beta hemolytic Streptococci, Clostridia, H. Influenzae, H. Pertussis, H. ducreyi, Brucella, K. pneumoniae, Vibrio comma* and *Donovania granulomatis*. The moderately sensitive organisms include *E. coli, Aerobacter, Salmonella, Shigella, B. anthracis, P. tularensis, P. pestis, Fusobacterium, Listeria monocytogenes* and *M. tuberculosis*. *Pseudomonas* is relatively resistant. Other organisms which respond satisfactorily are *Borrelia recurrentes, Mycoplasma pneumoniae (PPLO), Leptospira icterohaemorrhagiae* and *T. pallidum*. Actinomyces and Nocardia also respond but less than to penicillin. Amongst the

Martindale



(PhP)
Pharmaceutical Press

Tetracycline may interfere with some diagnostic tests including determination of urinary catecholamines or glucose.

Porphyria. Tetracyclines were considered to be probably safe in patients with acute porphyria, although there was conflicting experimental evidence of porphyrinogenicity, with results from *animals* or *in-vitro* systems suggesting that doxycycline or oxytetracycline might be porphyrinogenic.[1]

1. Moore MR, McColl KEL. *Porphyria: drug lists*. Glasgow: Porphyria Research Unit, University of Glasgow, 1991.

Interactions

The absorption of the tetracyclines is reduced by divalent and trivalent cations such as aluminium, bismuth, calcium, iron, magnesium, and zinc, and therefore concomitant administration of tetracyclines with antacids, iron preparations, some foods such as milk and dairy products, or other preparations containing such cations, whether as active ingredients or excipients, may result in subtherapeutic serum concentrations of the antibacterial. Sodium bicarbonate, colestipol, and kaolin-pectin are also reported to reduce tetracycline absorption, but potential reductions due to cimetidine or sucralfate are probably of little clinical significance.

The nephrotoxic effects of tetracyclines may be exacerbated by diuretics, methoxyflurane, or other potentially nephrotoxic drugs. Potentially hepatotoxic drugs should be used with caution in patients receiving tetracyclines. An increased incidence of benign intracranial hypertension has been reported when retinoids and tetracyclines are given together. Tetracyclines have been reported to produce increased concentrations of lithium, digoxin, and theophylline (although these interactions are not strongly established); the effects of oral anticoagulants may also be increased. There have been occasional reports of tetracyclines increasing the toxic effects of ergot alkaloids and methotrexate. Tetracyclines may decrease plasma-atovaquone concentrations. Ocular inflammation has occurred following the use of ocular preparations preserved with thiomersal in some patients receiving tetracyclines. Tetracyclines may decrease the effectiveness of oral contraceptives.

Because of possible antagonism of the action of the penicillins by predominantly bacteriostatic tetracyclines it has been recommended that the two types of drug should not be given concomitantly, especially when a rapid bactericidal action is necessary.

Antimicrobial Action

The group of tetracycline antibiotics is mainly bacteriostatic, with a broad spectrum of antimicrobial activity including chlamydias, mycoplasmas, rickettsias, and spirochaetes, and also many aerobic and anaerobic Gram-positive and Gram-negative pathogenic bacteria, and some protozoa.

Mechanism of action. Tetracyclines are taken up into sensitive bacterial cells by an active transport process. Once within the cell they bind reversibly to the 30S subunit of the ribosome, preventing the binding of aminoacyl transfer RNA and inhibiting protein synthesis and hence cell growth. Although tetracyclines also inhibit protein synthesis in mammalian cells they are not actively taken up, permitting selective effects on the infecting organism.

Spectrum of activity. The following pathogenic organisms are usually sensitive to tetracyclines.

Gram-positive cocci including some strains of *Staphylococcus aureus* and coagulase-negative staphylococci, and streptococci including *Str. pneumoniae*, *Str. pyogenes* (group A), some *Str. agalactiae* (group B), and some viridans streptococci. Enterococci are essentially resistant.

Other sensitive Gram-positive bacteria include strains of *Actinomyces israelii*; *Bacillus anthracis*; *Erysipelothrix rhusiopathiae*; *Listeria monocytogenes*, and among the anaerobes some *Clostridium* spp. *Nocardia* spp. are generally much less susceptible although some are sensitive to minocycline. *Propionibacterium acnes* is susceptible although the action of the tetracyclines in acne is complex and benefit may be seen even at subinhibitory concentrations.

Gram-negative cocci including *Neisseria meningitidis* (meningococci) and *N. gonorrhoeae* (gonococci). *Acinetobacter* spp., and *Moraxella (Branhamella) catarrhalis*.

Other sensitive Gram-negative aerobes include *Bordetella pertussis*, *Brucella* spp., *Calymmatobacterium granulomatis*, *Campylobacter* spp.; *Eikenella corrodens*, *Francisella tularensis*, *Haemophilus influenzae* and some strains of *Haemophilus ducreyi*, *Legionella*, *Pasteurella multocida*, *Streptobacillus moniliformis*, and various members of the Vibrionaceae including *Aeromonas hydrophila*, *Plesiomonas shigelloides*, *Vibrio cholerae* and *Vibrio parahaemolyticus*. Although many of the Enterobacteriaceae, including *Salmonella*, *Shigella*, and *Yersinia* spp., are sensitive, resistant strains are common; *Proteus* and *Providencia* spp. are not susceptible. *Pseudomonas aeruginosa* is not susceptible either, although some other species formerly classified as *Pseudomonas* respond, including *Burkholderia mallei*, *B. pseudomallei*, and *Stenotrophomonas (Xanthomonas) maltophilia*.

Among the Gram-negative anaerobes *Bacteroides fragilis* may sometimes be susceptible, although wild strains are often resistant, and *Fusobacterium* may also be sensitive.

Other organisms usually sensitive to tetracyclines include *Helicobacter pylori*, *Chlamydia* spp., *Rickettsia* and *Coxiella* spp., many spirochaetes including *Borrelia burgdorferi*, *Leptospira*, and *Treponema pallidum*, atypical mycobacteria such as *Mycobacterium marinum*, and mycoplasmas including *Mycoplasma pneumoniae* and *Ureaplasma urealyticum*. In addition the tetracyclines are active against some protozoa including *Plasmodium falciparum* and *Entamoeba histolytica*.

Fungi, yeasts, and viruses are generally resistant.

Minimum inhibitory concentrations (MICs) of tetracycline for the most sensitive organisms (*Streptococci*, *Neisseria*, sensitive *Shigella* and *Salmonella* spp., *Bacteroides fragilis*) range from about 0.25 to 2 µg per mL, but organisms with MICs up to about 4 µg per mL are considered sensitive. MICs for the other tetracyclines are generally similar, although minocycline, and to a lesser extent doxycycline, are somewhat more active *in vitro* against many susceptible organisms than the other tetracyclines.

Resistance. Resistance to the tetracyclines is usually plasmid-mediated and transferable; it is often inducible and appears to be associated with the ability to prevent accumulation of the antibiotic within the bacterial cell both by decreasing active transport of the drug into the cell and by increasing tetracycline efflux.

Unsurprisingly, given the widespread use of the tetracyclines (including as components of animal feeds, although this is now banned in some countries) resistant strains of the majority of sensitive species have now been reported. Resistance has increased particularly among Enterobacteriaceae such as *Escherichia coli*, *Enterobacter*, *Salmonella*, and *Shigella* spp., especially in hospital isolates, and multiple resistance is common. Staphylococci are commonly resistant, although doxycycline or minocycline are occasionally effective against tetracycline-resistant strains. Resistance is now also common among the streptococci, with reported resistance rates of 15 to 62% among group A, and even more among group B streptococci; resistance among pneumococci is reported to range from 3 to 23%, with multiple drug resistance becoming common. Emergence of high-level tetracycline-resistant strains of *Neisseria gonorrhoeae* is common in some areas. Frequent resistance is also seen in clostridia; and in *Bacteroides fragilis* (among more than 60% of isolates in some countries), while increasing resistance amongst *Haemophilus ducreyi* has limited the value of tetracyclines in chancroid.

As the genetic determinants of tetracycline resistant organisms have been elucidated it has become clear that the same or very similar genes are responsible for resistance in a number of different genera.[1] More than a dozen distinguishable resistance determinants have been described but most of these can be grouped into 3 major families, each of which presumably evolved from an ancestral determinant, possibly originally derived from tetracycline-producing *Streptomyces* spp. The families represented by classes A to E, and K and L, respectively both code for an active efflux system which keeps intracellular tetracycline concentrations below inhibitory values; the former family are common among Gram-negative genera, while the latter have only been found in Gram-positive organisms to date. A third family of determinants, represented by classes M and O, specifies resistance by a cytoplasmic factor which protects the ribosome. Other tetracycline resistance determinants have yet to have their mechanism identified. As more and more determinants are identified it is clear that they have evolved over millennia to serve some function in the bacterial cell; identification of that role might suggest steps to control their persistence and spread.

1. Levy SB. Evolution and spread of tetracycline resistance determinants. *J Antimicrob Chemother* 1989; 24: 1–3.

Pharmacokinetics

Most tetracyclines are incompletely absorbed from the gastro-intestinal tract, about 60 to 80% of a dose of tetracycline usually being available. The degree of absorption is diminished by the presence of divalent and trivalent metal ions, with which tetracyclines form stable insoluble complexes, and to a variable degree by milk or food. However, the more lipophilic analogues doxycycline and minocycline are almost completely absorbed (more than 90%), and they are little affected by food. Formulation with phosphate may enhance the absorption of tetracycline.

Administration of tetracycline 500 mg by mouth every 6 hours generally produces steady-state concentrations of 4 to 5 µg per mL, whereas with doxycycline a dose of 200 mg is sufficient to produce peak concentrations of about 3 µg per mL. Peak plasma concentrations occur about 1 to 3 hours after ingestion. Higher concentrations can be achieved after intravenous administration; concentrations may be higher in women than in men.

In the circulation, tetracyclines are bound to plasma proteins in varying degrees, but reported values differ considerably ranging from about 20 to 40% for oxytetracycline, 20 to 65% for tetracycline; about 45% for chlortetracycline, 35 to 90% for demeclocycline, 75% for minocycline, and about 80 to 95% for methacycline and doxycycline.

The tetracyclines are widely distributed throughout the body tissues and fluids. Concentrations in CSF are relatively low, but may be raised if the meninges are inflamed. Small amounts appear in saliva, and the fluids of the eye and lung; higher concentrations are achieved with more lipid-soluble analogues such as minocycline and doxycycline. Tetracyclines appear in breast milk where concentrations may be 60% or more of those in the plasma. They diffuse across the placenta and appear in the fetal circulation in concentrations of about 25 to 75% of those in the maternal blood. Tetracyclines are retained at sites of new bone formation and recent calcification and in developing teeth.

The tetracyclines have been classified in terms of their duration of action in the body, although the divisions appear to overlap somewhat. Of the 'short-acting' derivatives, chlortetracycline has a reported half-life of about 6 hours, oxytetracycline 9 hours; and tetracycline 8 hours, although reported values for the latter two range from about 6 to 12 hours. The 'intermediate-acting' tetracyclines, demeclocy-

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CHAPTER

48 ANTIMICROBIAL AGENTS

[*Continued*]

Tetracyclines, Chloramphenicol, Erythromycin, and Miscellaneous Antibacterial Agents

Merle A. Sande and Gerald L. Mandell

TETRACYCLINES

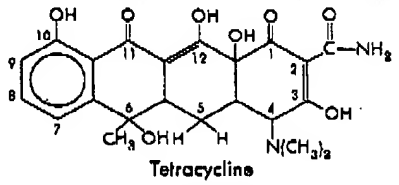
History. The development of the tetracycline antibiotics was the result of a systematic screening of soil specimens collected from many parts of the world for antibiotic-producing microorganisms. The first of these compounds, chlortetracycline, was introduced in 1948. Soon after their initial development, the tetracyclines were found to be highly effective against rickettsiae, a number of gram-positive and gram-negative bacteria, and the chlamydial species responsible for lymphogranuloma venereum, inclusion conjunctivitis, and psittacosis, and hence became known as "broad-spectrum" antibiotics. With establishment of their *in-vitro* antimicrobial activity, effectiveness in experimental infections, and pharmacological properties, the tetracyclines rapidly became widely used in therapy. (*See* Dowling, 1955; Lepper, 1956.)

Although there are specific and useful differences between the tetracyclines currently available in the United States, they are sufficiently similar to permit discussion of these drugs as a group.

Source and Chemistry. Chlortetracycline and oxytetracycline are elaborated by *Streptomyces aureofaciens* and *Strep. rimosus*, respectively. Tetracycline is produced semisynthetically from chlortetracycline; demeclocycline is the product of a mutant strain of *Strep. aureofaciens;* and methacycline, doxycycline, and minocycline are all semisynthetic derivatives.

The tetracyclines are closely congeneric derivatives of the polycyclic naphthacenecarboxamide. Their structural formulas are shown in Table 48–1.

Table 48–1. STRUCTURAL FORMULAS OF THE TETRACYCLINES



Tetracycline

CONGENER	SUBSTITUENT(S)	POSITION(S)
Chlortetracycline	—Cl	(7)
Oxytetracycline	—OH,—H	(5)
Demeclocycline	—OH,—H; —Cl	(6; 7)
Methacycline	—OH,—H; =CH_2	(5; 6)
Doxycycline	—OH,—H; —CH_3,—H	(5; 6)
Minocycline	—H,—H; —$N(CH_3)_2$	(6; 7)

Effects on Microorganisms. The tetracyclines possess a wide range of antimicrobial activity against gram-positive and gram-negative bacteria, which overlaps that of many other antimicrobial drugs. They are also effective against some microorganisms that are resistant to agents that exert their effects on the bacterial cell wall, such as *Rickettsia, Mycoplasma, Chlamydia* (the agents of urethritis, lymphogranuloma venereum, psittacosis, inclusion c njunctivitis, and trachoma), *Ureaplasma,* some atypical mycobacteria, and amebae. They have little activity against fungi.

In vitro, these drugs are primarily bacteriostatic. Only multiplying microorganisms are affected. The sensitivity or resistance of a particular microorganism to each of the congeners is similar. However, minocycline is usually the most active, followed by doxycycline. Tetracycline and oxytetracycline are the least active. Strains inhibited by 2 μg/ml or less of a tetracycline are considered sensitive.

Bacteria. In general, gram-positive microorganisms are affected by lower concentrations of tetracycline than are gram-negative species. However, these agents are rarely indicated for infections caused by gram-positive bacteria because of problems of resistance and the availability of superior antimicrobial agents. Most strains of group-B and group-D streptococci are not susceptible to tetracycline, while strains of *Staphylococcus aureus* remain mostly susceptible (Atkinson, 1986). Both tetracycline and doxycycline are quite active against most strains of pneumococci (minimal inhibitory concentration for 90% of strains [MIC 90] = 0.4 to

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86 | P wders

Particle siz reduction, classification, and measurement—mixing of powd rs—powd rs as a dosage form

This chapter was prepared by

Alvin Felmeister, PhD, *Associate Professor of Pharmacy, College of Pharmacy, Rutgers University, Newark, N.J. 07104*

Although there is no official definition of powders, this term generally refers to those pharmaceutical dosage forms that are made up of more or less finely divided, dry, solid material. The particle size of such powders may vary from the very fine, as in aerosols and insufflations, to the coarse, as in effervescent granules and some crude drug preparations. However, it should be noted that, in addition to constituting a class of pharmaceutical preparations, powders also serve as the starting point for other important dosage forms including tablets, capsules, and suspensions. While the use of powders as a dosage form has declined, the use of finely divided solid material in pharmaceutical manufacturing has become increasingly important.

With this has come the recognition of the influence of the particle size of these materials on the physical, chemical, and biological properties of the dosage form. The current literature is replete with studies that have served to establish relationships between particle size and dissolution, absorption, and therapeutic efficacy of drugs, particularly for those that are poorly or slowly soluble. Griseofulvin is probably the most dramatic and best documented example, although other equally important examples can be cited, such as the corticosteroids, insulins, and sulfonamides.

The influence of particle size on the physical and chemical properties of drugs and drug products also has been studied extensively. Flow properties, suspendibility, and compressibility of powders have all been related to particle size or surface area. The viscosity of suspensions have been modified by simply changing particle size or the charge on the particles. Furthermore, in a number of instances, chemical stability has been shown to be decreased markedly by the concomitant increase in surface area that results with particle size reduction. This is particularly true when the materials are sensitive to air oxidation or hydrolysis following water adsorption. Fincher[1] and Lees[2] have recently reviewed much of the literature in these areas.

Thus, since the importance of particle size in relationship to its influence on many properties of drugs and drug products has been well established, the methods of reducing, measuring, and controlling particle size must be considered of equal importance.

Particle Siz R ducti n

Comminution in its broadest meaning is the mechanical process of reducing the size of particles or aggregates. Thus, it embraces various operations such as cutting, slicing, chopping, rasping or grating, contusion, grinding, pulverizing, milling, micronizing, microatomizing, ball-milling, trituration, etc, depending primarily on the type of equipment or procedure employed. Some operations are performed primarily on crude drugs or vegetable materials, others on chemical substances. Vegetable substances offer varying degrees of resistance to comminution depending on the proportion and toughness of their ligneous fiber and the amount and kind of cellular tissue. Chemical substances vary in melting point, brittleness, hardness, and moisture content, all of which affect the ease of pulverization. As a result, many different machines and processes are employed to accomplish particular objectives.

Specifications for the finished product may differ depending on their end use. A granular, coarse, or fine powder may be required, or it may be necessary to reduce substances to specified particle size ranges, often in the micron, or subsieve, size. Special techniques and equipment are required to accomplish this, as well as to measure the state of subdivision.

Manual Methods and Equipment

Most of the comminution operations which were once used in pharmacy are rarely employed by the community pharmacist today. In the era when crude drugs and glandular materials were popular, the pharmacist had to prepare these substances in a proper state for extraction, or to reduce them to a powder. Now the pharmacist rarely employs the small-scale operations of cutting, chopping, rasping or grating, and the knives, cutters, graters and heavy contusion mortars have been largely supplanted by the prescription mortar and pestle, spatula, and on occasion the muller and slab with which most comminution and mixing procedures are presently conducted. With these, the pharmacist can reduce granular or crystalline chemicals to a fine powder or he can blend or mix several components into the homogeneous mixture required to assure uniformity of dosage in extemporaneously compounded prescriptions. If necessary, these techniques also can be used to reduce compressed tablets to a fine powder suitable for use in prescriptions.

The manually operated procedures usually employed by the prescription pharmacist today are *trituration*, *pulverization by intervention*, and *levigation*.

Trituration—This term refers to the process of reducing substances to fine particles by rubbing them in a mortar with a pestle. The term also designates the process whereby a mixture of fine powders is intimately mixed in a mortar. The circular mixing motion of the pestle on the powders contained in a mortar results in blending them and in also breaking up soft aggregates of powders. By means of the application of pressure on the pestle, crushing or grinding also can be effected.

When granular or crystalline materials are to be incorporated into a powdered product, these materials

Antibiotic and chemotherapy:

Anti-infective agents and their use in therapy

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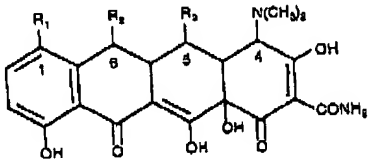
CHAPTER 35

Tetracyclines

R. G. Finch

Introduction

A group of natural products derived from Streptomyces *spp. and their semi-synthetic derivatives based on a hydronaphthacene nucleus containing four fused rings:*



The natural products include chlortetracycline, oxytetracycline, tetracycline and demeclocycline (demethylchlortetracycline). Semi-synthetic derivatives include methacycline, doxycycline, minocycline, clomocycline, lymecycline, rolitetracycline and the new investigational class of glycylcyclines. Closely related compounds include β-chelocardin, which lacks the $N(CH_3)_2$ group at position 4 and the thiacyclines which have sulphur in place of carbon at position 6.

Antimicrobial activity

Tetracyclines exhibit broad-spectrum activity which includes bacteria and protozoa. They are active against many common Gram-positive and Gram-negative bacteria, chlamydiae, mycoplasmas, rickettsiae, coxiellae, spirochaetes and some mycobacteria. They are generally inactive against fungi, although minocycline shows some activity against *Candida albicans*. They show useful activity against *Entamoeba histolytica* and plasmodia. In general, they are more active against Gram-positive than against Gram-negative bacteria. The hydrophilic congeners (e.g. tetracycline) are generally less active than the lipophilic congeners (e.g. minocycline and doxycycline). *Staphylococcus aureus*, including β-lactamase-producing strains, is susceptible, while coagulase-negative staphylococci are less predictably so. Most streptococci are susceptible, except *Streptococcus agalactiae* and enterococci. Other susceptible Gram-positive bacilli include *Actinomyces israelii*, *Arachnia propionica*, *Listeria monocytogenes*, most clostridia and *Bacillus anthracis*. Nocardia are much less susceptible, minocycline demonstrating the greatest activity.

Neisseriae and *Moraxella* (*Branhamella*) *catarrhalis*, including β-lactamase-producing strains, are susceptible, although resistant strains of *Neisseria gonorrhoeae* are ubiquitous and those of *Neisseria meningitidis* no longer uncommon. *Haemophilus influenzae* is susceptible, with doxycycline the most active agent, as are legionellae, brucellae and *Francisella tularensis*. Enterobacteria are generally susceptible, minocycline again being the most active compound. None of the tetracyclines has useful activity against *Proteus* spp., *Pseudomonas aeruginosa* or *Providencia* spp., but *Burkholderia* (*Pseudomonas*) *pseudomallei* and *Stenotrophomonas* (*Xanthomonas*) *maltophilia* are usually susceptible. Salmonellae and shigellae are susceptible, although resistant strains are now widespread, as are vibrios, *Campylobacter* spp., *Helicobacter pylori*, *Plesiomonas shigelloides* and *Aeromonas hydrophila*. Most anaerobic bacteria are susceptible, doxycycline and minocycline being most active, but wild strains of bacteroides are now commonly resistant.

Rickettsiae are more susceptible to doxycycline, minocycline and tetracycline than to other tetracyclines. Doxycycline and minocycline are often more active against common anaerobic bacteria in comparison with tetracycline and oxytetracycline. Approximately 90% of isolates are inhibited by 4 mg/l, with the exception of *Prevotella* (*Bacteroides*) *bivius* which appears more resistant. In the case of clostridia, doxycycline is more active than tetracycline; 96% of *Clostridium perfringens* are inhibited by 2 mg/l. Their activity is essentially bacteriostatic.